REMARKS

I. Preliminary Comments

Claims 97 and 98 have been amended to delete the recitation of "capable of providing a purified adenovirus composition for therapeutic use" and to substitute in its place the recitation "to provide a therapeutically acceptable composition."

In response to the notation regarding the Information Disclosure Statement of June 3, 2002 applicants resubmit a copy of the Japanese Patent (and English language Abstract) and Search Report which were not received by the Patent Office Examiner along with a form PTO-1449.

II. Outstanding Rejections

Claims 70-98 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-89 of Zhang et al., U.S. Patent 6,194,191.

Claims 70-98 are rejected under 35 U.S.C. § 112 (second paragraph) as being indefinite. More specifically, claims 72-78 and 94-96 are rejected under 35 U.S.C. § 112 (second paragraph) as being "incomplete for omitting essential steps" and for reciting "a purified adenovirus composition" and claims 97 and 98 stand rejected for reciting "suitable for therapeutic use."

Claims 70-98 are also rejected under 35 U.S.C. §112 (first paragraph) for failing to comply with the written description requirement. This rejection appears linked to the last indefiniteness rejection in that the Examiner states that "[t]he claims do not state the active steps used to obtain the desired pure product..."

Claims 70, 72-73, 75-77 and 80-97 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Shabram et al., U.S. Patent 5,837,520 (having a U.S. filing date of March 7, 1995 compared to the application's priority date of November 20, 1996) in view of Perrin et al., (Vaccine 13(13):1244-1250, 1995), Garnier et al., (Cytotechnology 15:145-155, 1994), and/or Nadeau et al., (Biotechnology and Bioengineering 51:613-623, 1996).

Dependent claims 78 and 79 directed to serum-free compositions and media are also rejected under 35 U.S.C. § 103(a) as being unpatentable over Shabram in view of Perrin, Garnier and/or Nadeau and further in view of Morris et al., (Williamsburg BioProcessing Conference, Nov. 18-21, 1996) or Gilbert (Williamsburg BioProcessing Conference, Nov. 18-21, 1996).

III. Patentability Arguments

The claims as amended above should be allowed for the reasons set out below. Not only are the claims unobvious over the cited prior art but each of those claims comply with the distinct statutory requirements of providing an adequate written description in the disclosure as required by 35 U.S.C. §112 (first paragraph) and each claim particularly points out and distinctly claims the subject matter regarded by applicants as being their invention as required by 35 U.S.C. §112 (first paragraph).

A. The Double Patenting Rejection Should be Withdrawn.

The rejection of claims 70-98 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-89 of Zhang et al., U.S. Patent 6,194,191 should be withdrawn in light of the Terminal Disclaimer submitted herewith. The Terminal Disclaimer is accompanied by the fee under 37 C.F.R. §1.20(d).

B. The Indefiniteness Rejection of Claims 70-98 Under 35 U.S.C. §112 (second paragraph) Should be Withdrawn.

The indefiniteness rejection of claims 70 through 98 under 35 U.S.C. §112 (second paragraph) should be withdrawn because the claims particularly point out and distinctly claim the subject matter of the invention. First, the rejection of dependent claims 97 and 98 should be withdrawn in light of the amendment deleting the recitation of "capable of providing a purified adenovirus composition for therapeutic use" and substituting in its place "to provide a therapeutically acceptable composition." This recitation would be understood by those of skill in the art because the level of purity required for therapeutic compositions is established by regulatory agencies such as the FDA. For example, the current proposed guidelines for pyrogenicity/endotoxin for human gene therapy are recommended for parenteral drugs to be an upper limit for endotoxin of 5 EU/kg body weight/dose as measured using the Limulus Amebocyte Lysate (LAL) assay. (See USFDA Guidance for FDA Review Staff and Sponsors, attached hereto as Exhibit A, IV. C. 2., pg. 16 of 29)

Further, the rejection of claims 72-78 and 94-96 as being incomplete should be withdrawn as the recited steps fully define the invention in a manner such that one of ordinary skill in the art may determine what is and what is not encompassed by those claims. Specifically, it is the recited steps that are the active steps that produce the end product with the characteristics recited in the claim. These steps comprise steps a) and b) which are drawn to a process of growing host cells in a media which is fed with nutrients in a specified manner which can be one of fed batch, perfusion or in automated roller bottles. The remaining steps of c) infecting the host cells with an adenovirus; d) lysing the host cells to provide a lysate and e) purifying the lysate by a process other than by cesium chloride density gradient further define the inventive method.

No other steps need be recited because this recitation meets the first purpose of the second paragraph of Section 112 which is to inform the public "of the boundaries of what constitutes infringement of the patent" (see MPEP 2173) and further meets the second purpose which is to define the invention so that compliance with the other criteria of 35 U.S.C. may be determined. Because there is no uncertainty as to what the claims do or do not cover, the rejection under 35 U.S.C. §112 (second paragraph) for indefiniteness should be withdrawn.

C. The Rejection of Claims 70-98 Under 35 U.S.C. §112 (first paragraph) Should be Withdrawn.

The rejection of claims 70-98 as lacking of written descriptive support should be withdrawn because the disclosure fully describes the subject matter of the claims and there is no question that applicants were in possession of their claimed invention at the time they filed their application.

Compliance with the written description requirement "involves the question of whether the subject matter of a claim is supported by [conforms to] the disclosure of an application as filed" (MPEP 2163.01) The requirement exists to ensure that the applicant was in possession of the invention now claimed "as of the filing date." (MPEP 2163.02)

The Examiner "has the initial burden of presenting by a preponderance of the evidence why a person of ordinary skill in the art would not recognize in an applicant's disclosure a description of the invention defined by the claims." (MPEP 2163 III. A.) and In re *Wertheim et al.*, 191 U.S.P.Q 90 at 97 (CCPA 1976) which further points out that "an originally filed claim is its own written description." The claims do state the active steps used to obtain the desired pure product and the Action has failed to set out reasons why one of ordinary skill reviewing applicants' disclosure would question whether Applicants were in possession of their claimed invention at the time of filing.

Finally, while not an element of the written description requirement; Applicants address the question raised in the Action regarding suitable purification means by which to practice the invention. While the specification teaches preferred modes by which each of the recited steps of the invention may be practiced Applicants' invention lies in carrying out all the steps of the claims together to obtain a purified adenovirus composition. Thus, the disclosure teaches at page 63, line 24 through page 72 line 9 and elsewhere that various modes of purification would be operative in practice of the invention and those of ordinary skill in the art would be capable of practicing the invention based on those teachings. While the Action observes that the genus of purification methods comprises many species, it fails to provide any rationale why one of skill would believe those species would be inoperative in practice of Applicants' invention.

In contrast with the lack of rationale why those of ordinary skill would not believe Applicants were in possession of the invention described in their claims, there is a "strong presumption" that an adequate written description is present in the specification as filed (MPEP 2163 II A citing *In re Wertheim* 191 USPQ 90, 96 (C.C.P.A. 1976)). Accordingly, the rejection for lack of written description rejection under 35 U.S.C. §112 (first paragraph) should be withdrawn.

D. The Rejection of Claims 70, 72, 73, 75-77 and 80-97 Under 35 U.S.C. §103(a) Over Shabram et al. US 5,837,520 In View of Perrin, Garnier and/or Nadeau Should be Withdrawn.

The rejection of claims 70, 72, 73, 75-77 and 80-97 Under 35 U.S.C. §103(a) over Shabram et al. US 5,837,520 in view of Perrin, Garnier and/or Nadeau should be withdrawn because Shabram, as the Examiner concedes, is directed to growing cells in batch mode and fails to teach the claimed method of providing nutrients to the host cells by perfusion, fed batch or automated roller bottles. Further, the secondary references do not provide an

incentive to modify the Shabram method so as to scale-up adenovirus growth using medium replacement and fed-batch conditions. Moreover, even if the secondary references would have taught to modify Shabram so as to improve yields (and they do not) it would not have been obvious to do so to improve the purity of the resulting product as provided by the present invention. This rejection is essentially identical to that overcome in co-owned U.S. Patent No. 6,194,191 and should be withdrawn for similar reasons.

The secondary references applied to modify the disclosure of Shabram should not properly be combined with Shabram because they are not directed to virus production, but rather, to protein production utilizing a virus. This is an important distinction because maximizing viral protein production is not necessarily consistent with maximizing viral replication as will be discussed below.

More specifically, the Perrin et al. reference relates to a rabies virus system quite distinct from adenovirus. The fact that Perrin et al. teach perfusion in the context of rabies virus production would in no way motivate the use of perfusion in the context of adenovirus production. The reason for this is that rabies virus is an enveloped "budding" RNA-based rhabdovirus whereas adenovirus is a DNA capsid based non-enveloped virus of an entirely different viral family - these viruses infect and grow differently and indeed replicate differently. Moreover, adenovirus is a very fragile virus as compared to viruses like rabies virus and one would not expect that it could be handled in anywhere near the same manner as rabies virus. Therefore, there would be no *a priori* expectations that the optimal conditions in one system would be optimal or even functional in another system.

More importantly, Perrin says nothing about advantages in terms of ease of purification and purity that one might obtain by providing nutrients in the manner specified

by the claims. This in itself is strong evidence of non-obviousness, and a finding that is in no way taught or suggested by Perrin et al.

The Nadeau et al. reference is similarly not considered relevant for the reason that it fails to teach or suggest that perfusion or other culture methods that involve exchange of media can provide a more readily purifiable adenovirus product.

Nadeau does experiments with maintaining glucose levels within certain defined ranges for the purposes of improving recombinant protein production, but this is unrelated to Applicants' invention which concerns producing recombinant adenovirus itself. Applicants' claims are indeed not related in any way to recombinant protein production. Moreover, there is no teaching or suggestion in Nadeau that maintaining glucose levels within a defined range would render the resultant adenovirus more readily isolated and capable of being more easily purified to a high degree of purity.

Similarly, the Garnier et al. reference is directed to improvements in recombinant protein production and not to producing adenoviral particles. Moreover, Garnier does not appear to teach or suggest that providing nutrients to host cells by perfusion or other culture methods involving exchange of media would provide particular advantages in the production of highly purified adenovirus.

Moreover, the secondary references actually teach away from Applicant's invention because they are directed to production of protein products and not toward reproduction of virus particles. Specifically, those of skill in the art would believe that the dedication of nutritional resources and energy toward protein production would detract from the production of adenoviral particles and that the recommendations of the secondary references would not be adopted by one trying to improve viral particle production.

For the foregoing reasons, and consistent with the withdrawal of the corresponding rejection in the grandparent application. Applicants respectfully submit that none of Perrin, Garnier or Nadeau would have been combined with Shabram in the manner suggested in the Action to arrive at Applicants' invention. Accordingly, the rejections over the combination of Shabram with Perrin, Garnier and Nadeau should be withdrawn.

E. The Rejection of Claims 78 and 79 Under 35 U.S.C. §103(a) Over Shabram, In View Of Perrin, Garnier and/or Nadeau and Further In View of Morris or Gilbert Should be Withdrawn.

The rejection of 78 and 79 depending from claim 70 should be withdrawn because neither Morris nor Gilbert make up for the deficiencies of Shabram and the other references discussed above with respect to independent claim 70 from which claims 78 and 79 depend. While Morris and Gilbert might disclose the production of adenovirus in cells adapted to serum-free media they do not suggest that doing so according to the practice of Applicants' invention would yield a product with improved purity as disclosed by Applicants. Because, they would not have motivated one to modify the teaching of Shabram the rejection of claims 78 and 79 should be withdrawn.

CONCLUSION

In view of the above amendment, applicants believe the pending application is in condition for allowance.

Respectfully submitted,

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